

PATENT COOPERATION TREATY

From the
INTERNATIONAL PROVISIONAL EXAMINATION REPORT

9 JUL 2004

To:

Anand and Anand Advocates
B-47 Nizamuddin East
110013 New Delhi
India

PCT

NOTIFICATION OF TRANSMISSION OF
INTERNATIONAL PROVISIONAL EXAMINATION
REPORT

PCT Rule 71(1)

29 JUN 2004

Applicant's or agent's file reference

I-3321P-159

IMPORTANT NOTIFICATION

International Application No.

PCT/IN2003/000383

International Filing Date

3 December 2003

Priority Date

3 December 2003

Applicant

BIRCON INDIA LIMITED et al

1. The applicant is hereby notified that the International Preliminary Examination Report (IPER) from this Office will be filed with the International Preliminary Examination Committee on 29 June 2004, as indicated in the international application.
2. A copy of the report and its annexes, stated as being transmitted to the International Bureau, for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau may prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

REMINDER

The applicant must enter the national phase before or on 30 October 2004 by performing certain acts (filing translations and paying national fees) within 3 months from the priority date or later in some Offices (Article 39(1) (see also the reminder sent by the International Bureau with Form PCT/IN/2003/6).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the International Preliminary Examination Report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEN At:

AUSTRALIAN PATENT OFFICE
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IAN DOWD

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PATENT COOPERATION TREATY
PCT
INTERNATIONAL PRELIMINARY EXAMINATION REPORT

Applicant or代理人/Reference PCT/IN2003/000383	FOR FURTHER ACTION	International Preliminary Examination Report International Patent Office - Australia
International Application No. PCT/IN2003/000383		International Preliminary Report on Patentability International Patent Office - Australia
International Priority Document(s) Priority date(s) and country		Priority document(s) and country
IPC Class(es) - PCT/IN2003		
Applicant BIOCON INDIA LIMITED et al.		
<p>1. Has international preliminary examination report been prepared by the International Preliminary Examining Authority and transmitted to the applicant according to Article 36?</p> <p>2. This REPORT consists of a total of 3 sheets, including the cover sheet.</p> <p><input checked="" type="checkbox"/> This report is also accompanied by ANNEXES, i.e. 3 sheets of the description, claims and/or drawings which have been amended and are the basis for this report, and extracts containing statements made before the Authority (see Rule 6(6) and Section 507 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of 3 pages.</p> <p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"> I <input checked="" type="checkbox"/> Basis of the report II <input type="checkbox"/> Priority III <input type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV <input type="checkbox"/> Lack of unit of invention V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability citations and explanations supporting such statement VI <input type="checkbox"/> Certain documents cited VII <input type="checkbox"/> Certain defects in the international application VIII <input type="checkbox"/> Certain observations on the international application 		

Date of submission of the demand

22 March 2004

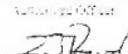
Date of completion of the report

22 June 2004

Name and mailing address of the IBA As

AUSTRALIAN PATENT OFFICE
PO BOX 2000, WOOLSTON, ACT 2601, AUSTRALIA
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I. Basis of the report

- With regard to the elements of the file number, the following is true:
- the international application was filed by []
- the description (pages 2-7, 28 pages) claims (pages 1-28) were filed on 18 June 2004 and the drawings (16 June 2004)
- the claims (pages 9-10, 2 pages) were filed on 18 June 2004 and the description (pages 1-28, 28 pages) and the drawings (16 June 2004) were filed on 16 June 2004
- the drawings (page 1, 2 pages) were filed on 16 June 2004
- pages 2-7, 28 pages, with the claims
- PCT/IN2003/000383 is the latest priority date
- the sequence listing part of the description:
- pages 1-28, 28 pages
- pages 1-28, 28 pages, with the claims
- pages 1-28, 28 pages, with the drawings
- With regard to the language, all the elements marked below were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item. These elements were available or furnished to this Authority in the following language(s), which is/are:
- the language of a translation furnished for the purposes of international search (under Rule 23.1(b))
- the language of publication of the international application (under Rule 48(6)(a))
- the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3)
- With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:
- contained in the international application in written form
- filed together with the international application in computer readable form
- furnished subsequently to this Authority in written form
- furnished subsequently to this Authority in computer readable form
- The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished
- The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished
- The amendments have resulted in the cancellation of:
- the description (pages)
- the claims. Not
- the drawings. Sheet, fig.
- This report has been established as follows: Of the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Search opinion box (Rule 70.2(c)). *
- *Applicant shall bear the costs of any further examination or opposition proceedings under Article 44(4) as referred to in the comments "Opposition Filing" and "Further examination or opposition proceedings" under Rules 70.16 and 70.17.
- An replacement sheet containing full and detailed information relating to the above points of the document is attached.

V Reasoned statement under Article 55(2) with regard to novelty, inventiveness or industrial applicability; citations and explanations supporting such statement

I Statement

Novelty (c)(i)	None - 1-10 None	YES NO
Inventive step (c)(ii)	None - 1-10 None	YES NO
Industrial applicability (c)(iii)	Claims - 1-10 Claims	YES NO

C Citations and explanations (Rule 76(1))

This report is based on the documents cited in the International Search Report.

- D1 US 5 508 398 A1
- D2 US 5 616 995 A1
- D3 US 4 734 492 A1
- D4 E Antibiot (rukvor) (1999 May 22) p. 306-73
- D5 US 6 576 145 B1
- D6 US 6 492 513 B1

Novelty and Inventive Step

None of the documents cited impinge on the application for the purposes of novelty or inventive step.

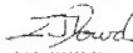
Industrial Applicability

All claims satisfy the requirements of industrial applicability.

PATENT COOPERATION TREATY
PCT
INTERNATIONAL PRELIMINARY EXAMINATION REPORT

PCT/IN/2003/000383

Applicant or agent file reference 11352(PCT/159)	FOR FURTHER ACTION See Section 19(1) of International Preliminary Report Form PCT/IPIA/160	Int'l filing Date 2 December 2003 Priority Date 3 December 2003
International Patent Classification (IPC) (or national classification) at filing date Int. CL. 7 C 04D 495/18		
Applicant BIDCO INDIA LIMITED et al		
1. This international preliminary examination report has been prepared by the International Preliminary Examining Authority and is transmitted to the applicant according to Article 35.		
2. This IPIER consists of a total of 3 sheets, including this cover sheet.		
<input checked="" type="checkbox"/> This report is also accompanied by ANNEXES, i.e. extracts of the description, claims and/or drawings which have been amended and are the basis for the subsequent direct continuing registrations made before this Authority (see Rule 70.16 and Section 60 of the Administrative Instructions under the PCT).		
These annexes consist of a total of 3 pages.		
3. This report contains indications relating to the following items:		
I <input checked="" type="checkbox"/> Basis of the report	II <input type="checkbox"/> Prior art	III <input type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV <input type="checkbox"/> Lack of unity of invention	V <input checked="" type="checkbox"/> Reasoned statement under Article 29(2) with regard to novelty, inventive step or industrial applicability, citations and explanations supporting such statement	VI <input type="checkbox"/> Certain documents cited
VII <input type="checkbox"/> Certain defects in the international application	VIII <input type="checkbox"/> Certain observations on the international application	

Date of submission of the demand 22 March 2004	Date of completion of the report 24 June 2004
Name and mailing address of the IPEX/DO	
AUSTRALIAN PATENT OFFICE PO BOX 200 WOOLNAT ACV 2605 ACT 2605 E-mail address: pcr@ipaustralia.gov.au Facsimile No: (02) 6283 3229	
 IAN DOWD Telephone No: (02) 6283 3273	

I. Basis of the report

1. With regard to the elements of the international application:
- the international application as originally filed
 - the description (pages 2-7, as originally filed, pages 1, filed with the demand, pages 1, received on 18 June 2004, filed on 16 June 2004)
 - the claims, (pages 9-10, as originally filed, pages 1, as amended, received on 18 June 2004, filed on 16 June 2004)
 - the drawings (pages 1, as originally filed, pages 1, filed with the demand, pages 1, received on 18 June 2004, with the demand, 16 June 2004)
 - the sequence listing part of the description (pages 1, as originally filed, pages 1, filed with the demand, pages 1, received on 18 June 2004)
2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item. These elements were available or furnished to this Authority in the following language(s) which is/are:
- the language of a translation furnished for the purposes of international search under Rule 13(1)(g)
 - the language of publication of the international application (see Rule 48,3(b))
 - the language of the translation furnished for the purposes of international preliminary examination under Rules 88.2 and/or 55.3)
3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:
- contained in the international application in written form;
 - filed together with the international application in computer readable form;
 - furnished subsequently to this Authority in written form;
 - furnished subsequently to this Authority in computer readable form.
- See also note to the heading under "Sequence listing" below. Sequence listing is not required for a nucleotide or an amino acid sequence which is furnished in accordance with Article 14(3)(a) of the Convention or Article 17(3) of the PCT if the international application as filed has been furnished.
- The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished
4. The amendments have resulted in the cancellation of:
- the description, pages
 - the claims, Nos.
 - the drawings, sheets/file
5. This report has been established as it stands¹ if the amendments did not been made, since they have been considered to go beyond the disclosing as filed, as indicated in the Supplemental Briefing, "A1, A2, A3".
- Replacement sheets which have been furnished in the course of the international preliminary examination under Article 14 are referred to in this report as "originally filed" and are referred to in this report as "as originally filed". See also Amendments Rule 50.16 and 70.17. The replacement sheet containing such amending matter is referred to in this report as "as provided in this report".

- V. Reasoned statement under Article 38(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement:

1. Statement

Novelty (N)	Claims 1-10	YES
	Claims	NO
Inventive step (IS)	Claims 1-10	YES
	Claims	NO
Industrial applicability (IA)	Claims 1-10	YES
	Claims	NO

2. Citations and explanations (Rule 70 (7))

This report is based on the documents cited in the International Search Report:

- D1 US 5 508 798 A
D2 US 5 676 595 A
D3 US 4 734 407 A
D4 J. Antibiot (Tokyo) 1999 May; 52(5): 489-73
D5 US 6 376 155 B1
D6 US 6 497 513 B1

Novelty and Inventive Step

None of the documents cited impinge on the application for the purposes of novelty or inventive step.

Industrial Applicability

All claims satisfy the requirements of industrial applicability.

5 **TITLE OF THE INVENTION**

PROCESS FOR THE PURIFICATION OF MACROLIDES

FIELD OF THE INVENTION

This invention relates to a process for purification of macrolides.

10 **BACKGROUND OF THE INVENTION**

A compound, 15,19-Epoxy-3H-pyrido[2,1-c][1,4]oxaaazacyclotricosine-1,7,20,21(4H,23H)-tetrone, 5,6,8,11,12,13,14,15,16,17,18,19,24,25, 26,26a-hexadecahydro-5,19-dihydroxy-3-[(1E)-2-[(1R,3R,4R)-4-hydroxy-3-methoxycyclohexyl]-1-methyl ethenyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-8-(2-propenyl)-, (3S,4R,5S,8R,9E,12S,14S,15R,16S,18R,19R,26aS), also known as FK506 as well as tacrolimus disclosed by EP 184162 and US 4,894,366 is useful as an immunosuppressant. Another compound, 15,19-Epoxy-3H-pyrido[2,1-c][1,4]oxaaazacyclotricosine-1,7,20,21(4H,23H)-tetrone,8-ethyl-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26, 26a-hexadecahydro-5,19-dihydroxy-3-[(1E)-2-[(1R,3R,4R)-4-hydroxy-3-methoxycyclohexyl]-1-methylethenyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-, (3S,4R,5S,8R,9E,12S,14S,15R,16S,18R,19R,26aS)-, also known as immunomycin as well as FK 520, disclosed in EPO Publication No. 0184162 is also useful as an immunosuppressant. Many other derivatives of these compounds as well as structural analogues have immunosuppressant property.

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5. We claim:

1. A process for the recovery of a macrolide in substantially pure form comprising:
 - a) treatment of an impure or crude macrolide with water immiscible solvent,
 - b) optional concentration of the mixture,
 - c) treatment with ammonia gas to phase out impurities,
 - d) separation of impurities,
 - e) optional concentration of the phase containing the macrolide,
 - f) loading on silica gel chromatography, optionally reversed phase or pretreated with silver, and elution of the macrolide,
 - g) affording the macrolide in substantially pure form,
 - h) optional repetition of step f and g to afford the macrolide in substantially pure form.
2. A process as in claim 1, wherein the macrolide is selected from tacrolimus, immunomycin or sirolimus.
3. A process as in claim 1, wherein the water immiscible solvent is selected from a group comprising hydrocarbons, heterocyclic compounds, ethers or esters.
4. A process as in claim 1, wherein the water immiscible solvents is selected from a group comprising benzene, toluene, hexane, ethyl acetate, isobutyl acetate or butyl acetate.
30. 5. A process as in claim 1, wherein the macrolide compound is afforded by crystallization or precipitation.